# Unexplained recurrent fever: when is autoinflammation the explanation?

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**Abstract**

Recurrent fever can be the sole or leading manifestation of a variety of diseases including malignancies, autoimmune diseases and infections. Because the differential diagnoses are manifold, no formal guidelines for the approach of patients with recurrent fever exists. The newly recognized group of autoinflammatory diseases are often accompanied by repetitive fever attacks. As these episodes are frequently associated by a variety of divergent presentations, the differentiation of other causes for febrile illnesses can be difficult. In this article, we first review disease entities, which frequently present with the symptom of recurrent fever. In a next step, we summarize their characteristic pattern of disease presentation. Finally, we analyse key features of autoinflammatory diseases, which are helpful to distinguish this group of diseases from the other causes of recurrent fever. Recognizing these symptom patterns can provide the crucial clues and, thus, lead to the initiation of targeted specific diagnostic tests and therapies.

**Abbreviations**
CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndrome; CINCA, chronic infantile neurologic cutaneous and articular syndrome; CRP, C-reactive protein; DIRA, deficiency of the interleukin receptor antagonist; DITRA, deficiency of Interleukin-36 receptor antagonist; HIDS, hyperimmunoglobulinaemia D with periodic fever syndrome; FCAS, familial cold autoinflammatory syndrome; FUO, fever of unknown origin; FMF, familial Mediterranean fever; IL-1β, interleukin-1β; IL-6, interleukin-6; MWS, Muckle–Wells syndrome; NOMID, neonatal onset multisystem inflammatory syndrome; PDC, potentially diagnostical clues; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; SAA, serum amyloid A; soJIA, systemic onset juvenile idiopathic arthritis; TNF-α, tumour necrosis factor-α; TRAPS, TNF receptor-associated periodic syndrome.

*'The rhythmic recurrence of disease is an age-old problem. It puzzled ancient physicians who supposed the rhythm to be controlled by cosmic influences…*

*A number of factors suggest a unity of periodic disorders: The cycles and episodes are of similar duration, they usually are benign, they often begin in childhood, recur unchanged for decades and heredity occasionally is evident. There is an overlapping of symptoms and signs in many of the disorders often great enough at times to confuse classification'* (from 'Periodic Disease' (1))

Recurrent fever is common and can be the most prominent symptom of various diseases. The conditions underlying recurrent fever are manifold, which is one of the reasons why no formal guidelines for an evidence-based approach to its management are currently available. As individual episodes of recurrent fever are often of short duration, many patients are symptom free when they are reviewed by specialists who may come from a variety of fields (e.g. paediatrics, immunology, rheumatology, infectious diseases, cardiology, haematology and dermatology). Thus, the evaluation of the patient is often biased towards the taken history and evidence of chronic damage rather than acute signs present only during symptomatic attacks.

Fever is characterized by a nonphysiological increase in body temperature due to an increased hypothalamic set point. It often accompanies infections and other pathological processes, where cytokines [e.g. interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6)] mediate an increase in the hypothalamic set point. To achieve a higher core temperature, the body changes its own heat production and heat loss mechanisms (2, 3).

No firm definition of recurrent fever is currently established. For reasons of practicability, the suggested definition by Knockaert, who defined recurrent fever by at least two episodes of fever separated by an (apparently) symptom-free interval of at least 2 weeks (4), will be applied in this article. This definition excludes, amongst others, conditions characterized by intermittent fever with fever episodes occurring with <2-week intervals. Examples of such a fever pattern are systemic onset of juvenile idiopathic arthritis (soJIA) presenting with a once-daily high spiking fever or in malaria as fever with definite short rhythm.

Autoinflammation has been identified as the principal pathogenic mechanism underlying a variety of diseases characterized by a cytokine-mediated apparently unprovoked recurrent inflammatory reaction (see Box 1) (5). Recurrent fever attacks are one of the hallmark features of these diseases, and as a result, some autoinflammatory syndromes – particularly those also known as hereditary fever syndromes – are important diagnoses to consider in patients with recurrent fever. As many of these disorders are extremely rare, most physicians are not familiar with them.

**Box 1**

**Definition of autoinflammation**

- Autoinflammatory diseases are clinical disorders characterized by abnormally increased inflammation and mediated predominantly by effector cells and molecules of the innate immune system. In a predisposed host, as demonstrated for the 'classical' monogenic autoinflammatory disorders, known exogenous and endogenous factors precipitate the inflammatory attacks (5).
- Recurrent hereditary fever syndromes are often considered as 'classical' autoinflammatory diseases and are caused by known molecular mechanisms. In other autoinflammatory disorders, such as Still's disease and Schnitzler's syndrome, aetiology is more complex and mostly unknown. In many other diseases, for example gout or diabetes, autoinflammatory mechanisms are proposed to crucial contribute to the pathology.

In this article, we offer a guide on when to think of an autoinflammatory disease as the cause of recurrent fever of unknown origin (FUO) and give an overview of the major recognized syndromes. Many of these syndromes display characteristic clinical patterns, which can be very helpful in identifying patients.

## General causes of recurrent fever

Many inflammatory and also noninflammatory conditions can lead to a recurrent 're-setting of the body thermostat', with the consequence of a recurrent increase in body core temperature (Table 1).

Out of these, the 'big three' comprise infection, malignancies and noninfectious inflammatory disease (4).

*(Systemic) infections* classically lead to fever. In four different scenarios, infections can also be the cause of recurrent fever instead of continuous fever:

1 *Insufficiently treated infection,* for example, by an incorrect antibiotic or too short a course of treatment.
2 *One single persisting infection causing recurrent fever episodes;* this scenario is possible when the infectious agent causes a chronic infection, produces virulence factors or escapes the host defence mechanisms. *Spirillum minor* as well as *Borrelia recurrentis* and *B. duttoni* exhibit these properties and are responsible for relapsing fever attacks. Other persistent infections are rarely described as a cause of recurrent fever in immunocompetent individuals (see Box 2 in the Appendix) (6–8).
3 *The host exhibits an enhanced susceptibility to infections,* as in the case of anatomical malformations or classically in primary and secondary immunodeficiencies (9).
4 Especially in young childhood, a *physiological susceptibility to infections* is frequently observed. In an immunocompetent child up to 11 minor mostly viral infections

**Table 1** Disease groups causing recurrent fever

| | Big three | | | | Little three | | | Miscellaneous |
|---|---|---|---|---|---|---|---|---|
| Mechanism | Inflammatory, infectious | Inflammatory, noninfectious | | Mostly inflammatory | Mostly noninflammatory, mostly no fever per definition | | | Various mechanisms |
| Disease (groups) | Infections | Autoimmune diseases | Autoinflammatory disease | Malignancies | Munchausen (by proxy) | Drug fever | Benign hyperthermia | E.g. central fever, dehydration |

Groups of inflammatory and noninflammatory conditions potentially leading to recurrent fever.

*per year* can occur (10). This is by far the most common reason for recurrent fever in this age group.

In *malignancies,* a variety of mechanisms, for example, the production and release of cytokines by necrotic material and batch-wise growing tumour cells are proposed to induce recurrent fever (11). Especially in lymphomas and leukaemias, which often present with B symptoms, elevated levels of the endogenous pyrogens IL-1β and IL-6 were observed (12).

*Noninfectious inflammatory diseases* are a diverse group of disorders, of which the autoimmune diseases are the best recognized. Autoimmune diseases are classically thought to induce antigen-specific proinflammatory processes, which subsequently may result in the development of fever. Intermittent courses, especially at disease onset, are frequently observed, and thus, these diseases have to be considered in patients with recurrent fever of unknown sources.

This group also comprises the autoinflammatory diseases, which are the main subject of this article. Autoinflammatory diseases are characterized by an often unprovoked cytokine-driven inflammatory process, mediated by cells of the innate immune system (see Box 1). Clinical features of these diseases have recently been reviewed in detail (13–15). As recurrence of fever is one hallmark of a subgroup of autoinflammatory syndromes, this group was also designated as *hereditary fever syndromes* (Table 2). Within these diseases, the fever can differ in terms of type, duration, frequency, periodicity, first onset, potential triggers and the associated symptoms (Table 2). This will be discussed in more detail below.

In addition, there are also three other groups recognized in FUO. These 'little three' comprise benign hyperthermia, factitious fever and drug fever (4).

In benign hyperthermia, the increase in body temperature is due to an imbalance of heat production and heat loss mechanisms with no change in the hypothalamic set point. Thus, it does not fulfil the definition of fever (2). Given that this condition can be observed frequently even in young children, it is an important differential diagnosis in patients with recurrent temperature increase (16).

Auto- (Munchausen syndrome) or allo-aggression (Munchausen by proxy) can include factitious fever with recurrent occurrence and thus must be considered in adults and children, respectively, with recurrent fever of unknown source (17, 18).

Drug fever is an often-overlooked cause for fever; it occurs as the sole or most prominent feature in about 3–5% of adverse events in hospitalized patients (19). Pathophysiological mechanisms of drug-induced fever have previously been reviewed (20). Although drug fever is usually characterized by a continuous fever, it can be recurrent, especially in multi-drug using patients.

## How to approach recurrent fever patients

Patients with recurrent fever of unknown source are often difficult to diagnose. The differential diagnoses are manifold, and therefore, an algorithm covering all possible causes appears difficult, if not impossible, to construct.

Prospective studies from the Netherlands have provided valuable lessons in the diagnostic approach to patients with (nonrecurrent) FUO (21, 22). These studies demonstrated that a carefully taken history, repeated physical examinations and a restricted set of investigations can lead to *potential diagnostic clues* (PDC). These clues include signs, symptoms and abnormalities, which potentially point towards the underlying cause and thus guide more specified tests.

In contrast to patients with FUO, the evaluation of patients with recurrent fever often necessitates a different approach since: (i) patients often consult a specialist during an attack-free period, thus signs of acute inflammation might not be present; (ii) the patient usually has a long history and many previous diagnostic (and probably therapeutic) attempts have failed to provide a conclusive explanation for the presented symptoms; and, most importantly, (iii) episodes may be characterized by a specific pattern. Recognition of these characteristic patterns together with a limited number of obligatory investigations provides relevant clues for the origin of recurrent fever (see below), which can then guide the choice of specific diagnostic tests.

## Pattern recognition in recurrent fever of unknown origin

Asking the right questions can identify patterns of recurrent fever manifestations. The following list of questions will support a systematic approach to the differential diagnosis.

1 At what age did symptoms first appear?
2 What is the duration of the individual fever episodes?
3 What other symptoms are associated with the fever episodes?
4 What is the time interval between episodes (duration, variable or fixed intervals)?
5 What can trigger or alleviate a fever episode?
6 How have symptoms developed over time?
7 Which treatments have been used and what was the response?
8 Is there a family history; does the patient originate from a certain ethnicity?

**Table 2** Characteristics of autoinflammatory syndromes with recurrent fever

| Disease | | Gene | Three main associated findings | Fever | |
|---|---|---|---|---|---|
| | | | | Onset | Duration |
| FMF | | *MEFV* | Peritonitis<br>Arthritis<br>Pleuritis | First years of life | 12–72 h |
| HIDS | | *MVK (mevalonate kinase)* | Lymphadenopathy<br>Arthralgias<br>Abdominal symptoms | First year of life | 3–7 days |
| CAPS | FCAS | *NLRP3/CIAS1* | Cold-induced urticarial rash<br>Arthralgias<br>Conjunctivitis | First year of life | Median 12 h |
| | MWS | | Urticarial rash<br>Sensorineural hearing loss<br>Amyloidosis | Childhood | If present 2–3 days |
| | NOMID | | Neonatal onset exanthema<br>Neurologic symptoms<br>Arthropathy with exostosis | Neonatal | If present varying duration |
| TRAPS | | *TNFRSF1A* | Migrating exanthemas and myalgias<br>Periorbital oedema and conjunctivitis<br>Peritonitis | First years of life | Days–weeks |
| CANDLE (83, 84) | | *PSMB8* | Atypical neutrophilic dermatosis<br>Lipodystrophy<br>Delayed physical development | First weeks to month of life | Daily – high frequent recurrent fever |
| DITRA (85–88) | | *IL36RN* | Generalized pustular psoriasis<br>General malaise<br>Hyperleucocytosis | Variable | Variable |
| NLPR12-associated periodic fever syndrome (89, 90) | | *NLRP12* | Cold-induced episodes<br>Arthralgias<br>Urticarial rash | First year of life | 2–10 days |
| Schnitzler's' syndrome | | None | Urticarial rash<br>IgM or IgG paraproteinemia<br>Bone pain | >50 years | Mostly 1–3, but varying |
| PFAPA | | None | Aphthous ulcer<br>Cervical adenitis<br>(Sterile) pharyngitis | Median 4th year of life | Median 4 days |
| soJIA | | None | Arthritis<br>Rash<br>Serositis, lymphadenopathy, organomegaly | 75% before 10th year of life | Weeks |
| AOSD | | None | Arthralgias<br>Rash<br>Sore throat, lymphadenopathy, splenomegaly | 75% before 50th year of life | Weeks |

FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinaemia D with periodic fever syndrome (Mevalonate kinase deficiency); CAPS, cryopyrin-associated periodic syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal onset multisystem inflammatory syndrome; TRAPS, TNF receptor-associated periodic syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; DITRA, deficiency of interleukin-36 receptor antagonist; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; soJIA, systemic onset juvenile idiopathic arthritis; AOSD, adult onset Still's disease; DIRA, deficiency of the interleukin 1 (IL-1) receptor antagonist; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne.

Only single cases of patients with CANDLE-, DITRA- and NLRP12-associated fever syndrome were described in the literature. These three diseases are not discussed in detail in the text. Autoinflammatory syndromes not typically associated with recurrent fever (e.g. DIRA, PAPA) are not mentioned in the table.

FCAS, MWS and NOMID show many phenotypical overlaps and are all caused by mutations in the *NLRP3* gene (*cyropyrin*), and thus these entities are combined as CAPS.

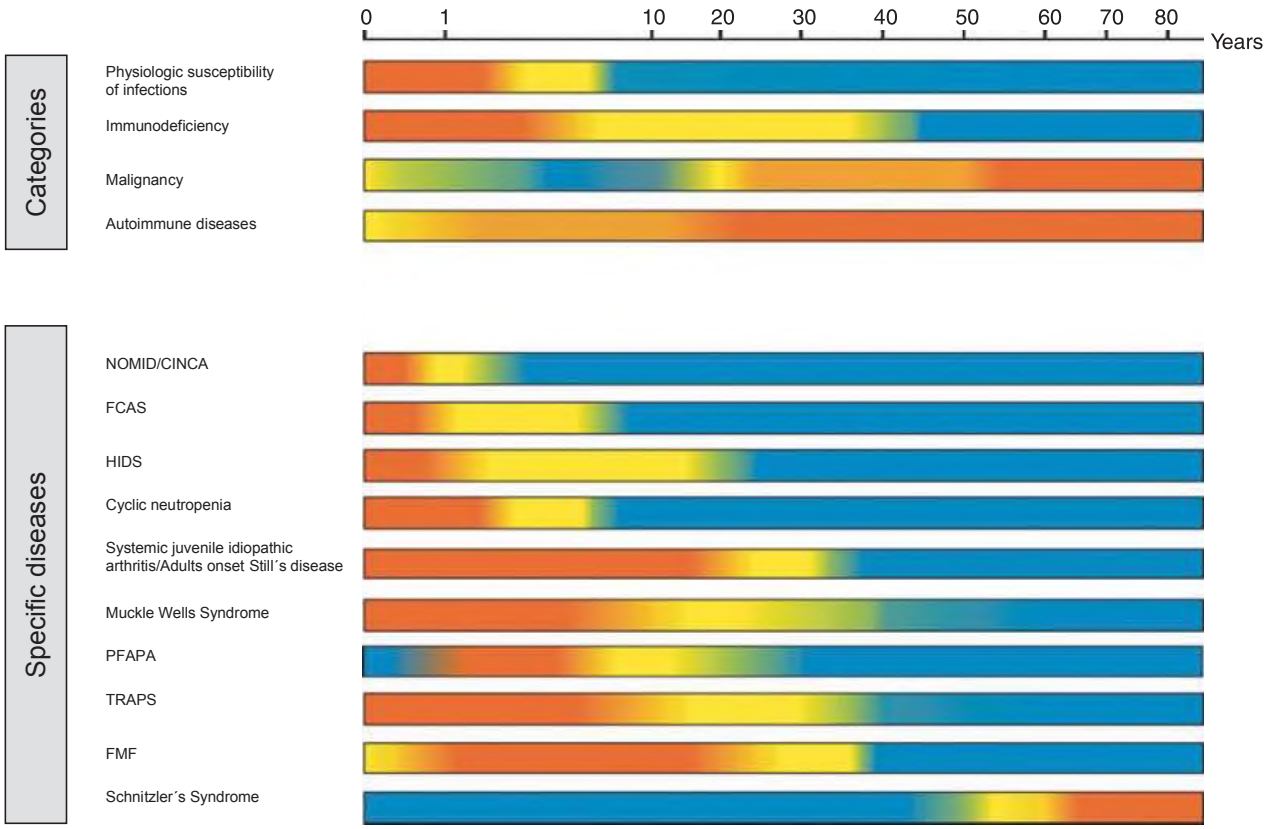


**Figure 1** Age of disease onset. Age distribution of disease onset according to disease groups (A) and specific diseases (B). Red symbolizes likely, yellow possible and blue unlikely age of disease manifestation. Systemic lupus erythematosus, dermatomyositis and polymyositis, mixed connective tissue disease and polymyalgia rheumatica are summarized as autoimmune diseases. Cyclic neutropenia is included, because it is a rare but important immunodeficiency, which mimics periodic fever syndromes and periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA).

### At what age did symptoms first appear?

In the young child, recurrent fever episodes are most likely caused by the physiological susceptibility to infections. Usually signs of minor infections accompany these episodes; the recurrent symptoms resolve during the first year of life without any sequelae (Fig. 1A) (10). Febrile episodes in patients with an inherited immunodeficiency usually also manifest first in the (very) young child, but they are frequently accompanied by severe infections not uncommonly caused by opportunistic pathogens. Nonetheless, approximately 20% of cases of primary immunodeficiency are diagnosed in adulthood (23). In children, malignant disease, particularly leukaemias [which are known to induce the synthesis of pyrogenic interleukins (12)], neuroblastoma, retinoblastoma and renal tumour, is most prevalent in the under 4-year-old age group; after the 10th year of life, the prevalence of malignancy then increases during the whole life span (24, 25). In childhood and early adulthood, systemic lupus erythematosus is a common autoimmune disease accompanied by fever; in later adulthood different systemic vasculitides, for example, polymyalgia rheumatica also frequently present with fever.

Most autoinflammatory diseases first manifest during early childhood. But late onset of symptoms, in adolescence or later, is seen in some patients (26–30).

### What is the duration of individual fever episodes?

Although the length of a single febrile episode can vary between and within individuals, fever duration can be helpful in pattern recognition. In patients with physiological susceptibility to infections, fever episodes are generally short (3–5 days) and also depend on the disease-causing infectious agents. In contrast, fever episodes in patients with immune deficiencies, autoimmune diseases and malignancies are usually of a longer duration (Fig. 2A).

Although autoinflammation can produce fever of almost any duration, individual autoinflammatory disorders are often associated with inflammatory episodes of characteristic durations (see next section).

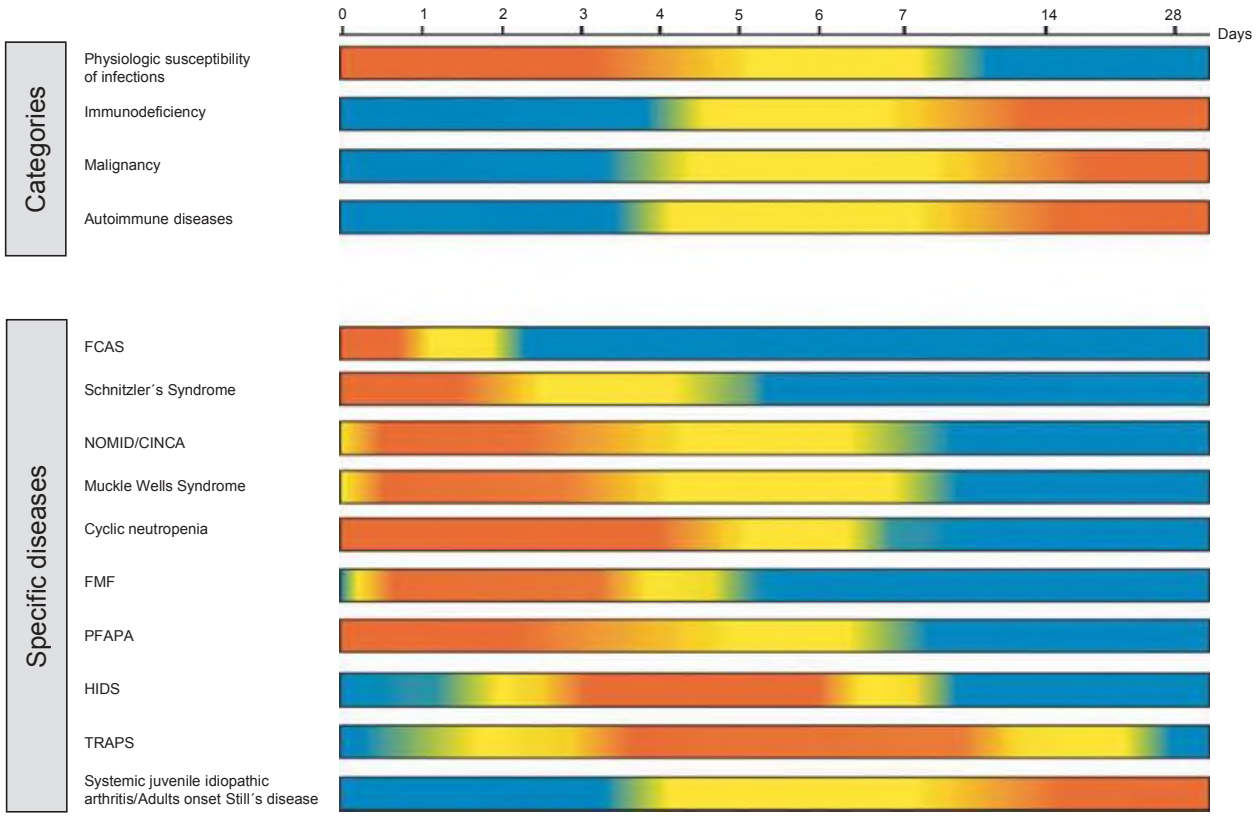


**Figure 2** Duration of fever attack. Average duration of febrile attacks according to disease groups (A) and specific diseases (B). The colours symbolize the likelihood as described in Fig. 1.

### What other symptoms are associated with the fever episodes?

As shown in Fig. 3A, a variety of associated symptoms can be helpful in classifying different disease groups. Recurrent minor infections are usually associated with mild symptoms only; malignancies are often accompanied by the occurrence of B symptoms (besides fever weight loss, night sweats); and autoimmune diseases frequently involve multiple organs. Accompanying symptoms can also point to certain autoinflammatory disorders.

### What is the time interval between episodes (duration, variable or fixed intervals)?

Usually, febrile episodes occur with varying time intervals and are rather episodic than strictly periodic. Only rarely the time interval is fixed, meaning that the symptom-free periods are always of the same length. This phenomenon is usually only observed in patients with cyclic neutropenia (31, 32) or with periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome (33, 34).

It is also important to ask whether patients are completely symptom free between the febrile episodes, or whether some symptoms persist. Persistent symptoms are more likely in case of malignancy or autoimmune disease. In many autoinflammatory diseases, patients can be completely symptom free in the intervals, although in some diseases, symptoms may persist.

### What can trigger or alleviate a fever episode?

This question can be helpful in the identification of many diseases and is especially important in patients with recurrent infections or drug-induced fever.

### How have symptoms developed over time?

A general worsening of the symptoms over time with an increasing number of organ systems affected and generally reduced well-being are more likely in autoimmune diseases or malignancies. Although organ damage can eventually develop over time in autoinflammatory diseases, the symptom complex accompanying the febrile attacks remains usually fairly constant.

### Which treatments have been used and what was the response?

Here, the response to antibiotics as well as anti-inflammatory and immunosuppressant therapy is of special interest and should be meticulously enquired about.

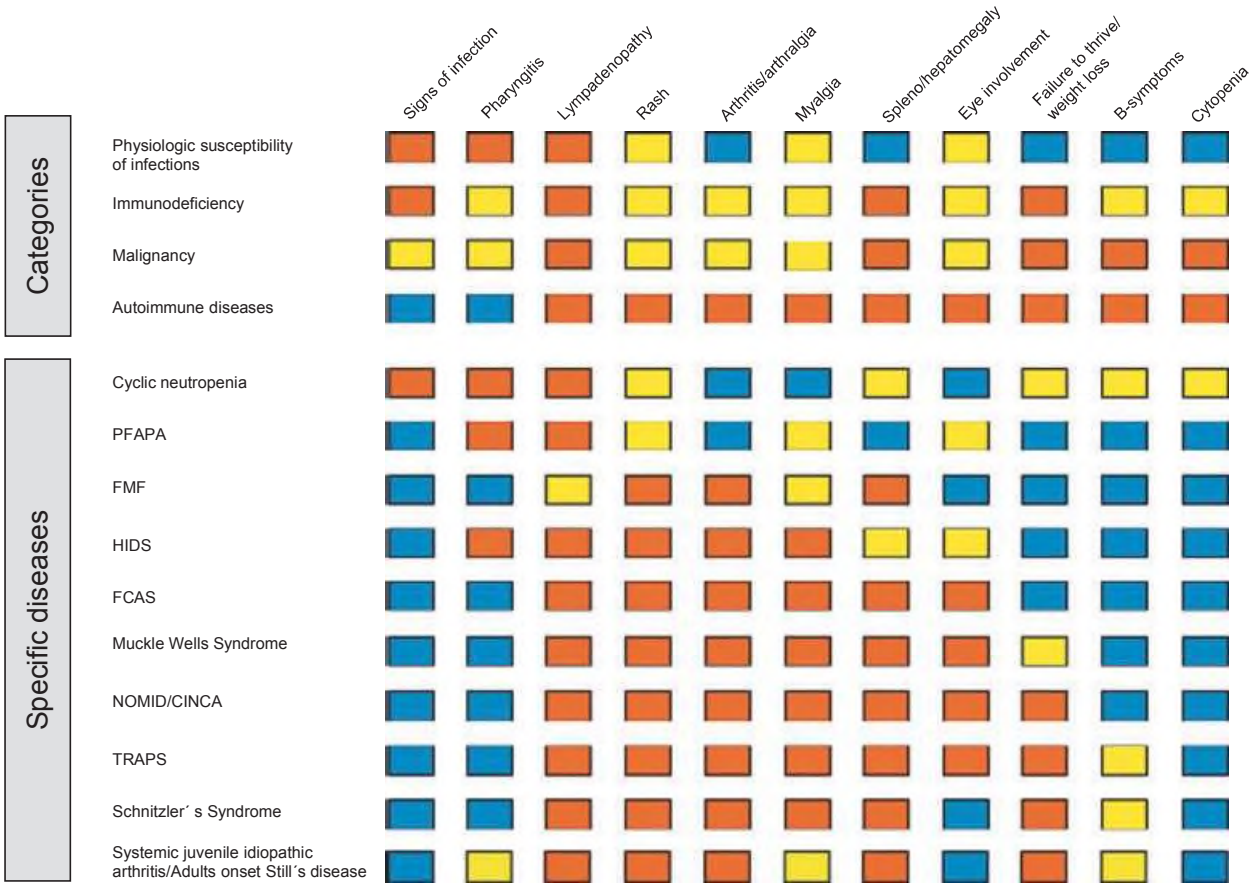


**Figure 3** Associated symptoms according to disease groups (A) and specific diseases (B). The colours symbolize the likelihood as described in Fig. 1.

### Is there a family history; does the patient originate from a certain ethnicity?

Recessive and dominant inheritance is well recognized in immune deficiencies and autoinflammatory diseases. Autoinflammatory disease especially segregates in certain ethnicities (see below).

## Distinguishing between the different autoinflammatory diseases using the above questions

The recognition of a pattern can be the first and most important step to suspect and, later on, to diagnose an autoinflammatory disease.

### First onset of symptoms is in early childhood

In 90% of patients, symptoms of Familial Mediterranean fever (FMF) start before the age of 20, in 75%, first symptoms are present before the age of 10 (35) (Fig. 1A).

The age of onset in cryopyrin-associated periodic syndromes (CAPS) depends on the phenotype: *per definition* first symptoms of neonatal onset multisystem inflammatory disease (NOMID) – also known as chronic infantile neurologic cutaneous and articular syndrome (CINCA) – start in the neonatal period, but recurrent fever episodes may not be the dominant feature. In 60% of cases, fever in patients with familial cold autoinflammatory syndrome (FCAS) manifests during the first days of life, and in nearly all patients, first symptoms are present during the first half year (36, 37) Nearly 90% of Muckle–Wells syndrome (MWS) cases present in infancy (30, 38). Febrile symptoms of hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) also start in early childhood, on average around the 6th month of life, and disease onset during the first weeks of life has been reported (39). Although first symptoms of TNF receptor-associated periodic syndrome (TRAPS) occur at a mean age of 3 years, first manifestations can occur anytime between the neonatal period and adulthood (29). Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome syndrome patients usually exhibit first symptoms before their 5th birthday with a wide range of disease onset (1/4–12 years) (40). Seventy-five per cent of patients with soJIA have their first symptoms before the 10th year of age. Adult onset Still's disease (AOSD) is usually manifests during young adulthood

(75% below the 50th year of age). Schnitzler's Syndrome is a classical example of an autoinflammatory disease characterized by recurrent fever, which only manifests in adulthood (mean age of onset is 50 years) (41).

### Duration of fever episode

In FMF, a main diagnostic criterion is the recurrence of short attacks with a duration of 12–72 h (42) (Fig. 2B). Short episodes are also observed in FCAS with a mean duration of 12 h and a range of 1/2–72 h (36). In HIDS and PFAPA, longer episodes of about 3–7 days are more common (33, 34, 43). In TRAPS, episodes frequently last for up to 3 weeks. Here, associated fever is only present during the first days and can be absent, particularly in adult patients (29). In patients with MWS and NOMID, the length of symptomatic episodes can vary, and fever is not found consistently. In Schnitzler's, syndrome, recurrent fever is commonly present for 1–3 days, but the pattern is variable (41). In soJIA and AOSD, fever episodes usually continue to occur for several weeks.

### Accompanying symptoms

Familial Mediterranean fever is generally associated with a rather limited but specific combination of symptoms caused by serositis at different sites (peritonitis, pleurisy and arthritis). In other autoinflammatory conditions, specific symptoms and signs, such as sensorineural hearing loss in CAPS, migratory myalgia in TRAPS, headache, mental retardation and arthropathy with exostosis in CINCA/NOMID, can be important diagnostic markers (Fig. 3C and Table 2). In soJIA and AOSD fever, the typical transient salmon-pink coloured rash can be the crucial diagnostic hint.

### Time interval between fever episodes

Cyclic neutropenia (31, 32) or a PFAPA syndrome should be considered when symptom-free periods are (almost) always of the same length (33, 34). Whereas young children with PFAPA often experience attacks every 3–4 weeks, adults with persistent symptoms experience fewer attacks (33, 34, 44). A high frequency of attacks, for example every other week, can be seen in FMF, but patients with symptom-free intervals of years or even no (febrile) symptoms have also been described (phenotype II FMF) (35, 45). In patients with other autoinflammatory diseases, attacks usually occur at longer time intervals and the frequency may also be influenced by the presence of triggering factors.

### Specific triggers are characteristic for certain autoinflammatory diseases

In general, in all autoinflammatory disorders, inflammatory episodes can be precipitated by emotional stress, exercise and (minor) infections, as well as fatigue (29, 39, 43). Female patients often notice a relationship with their menstrual cycle, and characteristically, fever episodes in most of the autoinflammatory disorders occur less frequently during pregnancy, but delivery often provokes an attack (46).

Some triggers may be more disease specific. Most importantly, cold can trigger symptoms in FCAS and MWS patients (36, 47). Fever episodes triggered by active immunization are frequently observed in HIDS (39, 43).

Current data derived from comprehensive biochemical analyses in PFAPA patients suggest that exposure to environmental agents, for example otherwise not pathogenic bacteria or viruses or parts of them, induces inappropriate inflammatory responses leading to recurrent febrile episodes in PFAPA patients (48).

### Development of symptoms over time

The course of the disease should be analysed from two different perspectives: (i) the characteristics and frequency of individual attacks and (ii) the development of long-term consequences.

Young children with FMF often present with signs of recurrent fever only, and other typical features of the disease such a relapsing serositis appear as they get older (49). In HIDS, a significant decrease in attack frequency with increasing age is observed, although attack frequency often increases just after adolescence (39). Fever is a typical symptom in children with TRAPS but may be absent during attacks in adults (29). Long-term follow-up of children with PFAPA showed that most patients improve over time and eventually show complete remission with a mean duration of disease of 6 years. In patients with long disease duration, the frequency of febrile episodes decreased significantly overtime (44). For the group of CAPS, for example, FCAS, MWS and NOMID, no synoptic data on age-related characteristics of the single episodes are available, but in general, acute symptoms seem not to differ over time.

All (untreated) monogenic autoinflammatory fever syndromes are associated with the development of AA amyloidosis, although the prevalence varies from very rare [in FCAS and HIDS (34, 37)], 14% in TRAPS (50), 25% in FMF (45) to approximately 30% in MWS (51). There are no reported cases in NOMID, presumably because before modern treatment few patients lived long enough to develop this complication. Cryopyrin-associated periodic syndrome-associated long-term consequences include sensorineural hearing loss in MWS and NOMID and visual loss and meningitic headaches as well as arthropathy with exostosis in NOMID (Table 2). These specific symptoms can be the crucial hint in making the right diagnosis.

### Response to treatment

Inefficacy of antibiotics is often a clear clue for an autoinflammatory aetiology. Steroids will have some benefit in many of the autoinflammatory diseases, although in general it is only very effective in PFAPA, soJIA and AOSD and to a lesser extent in HIDS (33, 34). Steroids have no beneficial effects in classical FMF attacks (45). Response to adequate colchicine therapy can confirm FMF (52). In many autoinflammatory disorders, specific IL-1 inhibitors induce dramatic and complete resolution of signs and symptoms (53–56).

### Family history and ethnicity

Familial Mediterranean fever should be especially considered in patients originating from countries of the eastern Mediterranean basin, for example Israel, Turkey and Armenia (57), but it also can occur in patients from other ethnicities (58, 59). Hyperimmunoglobulinaemia D with periodic fever syndrome is most prevalent in the Netherlands, Italy and France. The majority of patients from other countries were European or from European ancestry, but this may be likely an ascertainment bias, reflecting the availability of diagnostic testing (39). The other monogenic autoinflammatory diseases can be found in patients from all over the world.

A family history may reveal the inheritance pattern, which will point towards the right diagnosis. But a number of aspects are important: (i) the disease penetrance may vary, that is, not all mutation carriers are affected, (ii) especially in NOMID, many patients harbour a *de novo*-mutation, thus no other family member is affected (60) and (iii) there may be variable expressivity, that is, individuals may present with different symptoms of varying severity at a variable age of onset, and milder disease presenting later may be missed in a routinely taken history.

## Next diagnostic steps if an autoinflammatory syndrome is suspected

### Acute phase response

In autoinflammatory diseases, inflammatory febrile episodes are always accompanied by elevated levels of hepatic acute phase proteins and leucocytosis. Subclinical inflammatory responses can be detected in the symptom-free intervals in many instances (61–63). Signs of chronic inflammation, for example organomegaly, growth retardation or chronic anaemia, can occur. The discrepancy between highly elevated C-reactive protein (CRP) and low to normal procalcitonin is characteristic for PFAPA and FMF (64, 65). The phagocyte-specific danger signals S100A8/9 and S100A12 are sensitive biomarkers for the detection of (subclinical) inflammation in patients with FMF, soJIA and CAPS; in certain circumstances, they might be superior to classically used markers (66, 67). Ferritin levels are especially helpful in diagnosing patients with soJIA and AOSD. Greatly elevated levels may point to the life-threatening complication of a macrophage activation syndrome.

### Specific biochemistry markers

Slight increases in IgD serum concentrations can be found in a number of autoinflammatory disorders as well as other inflammatory diseases. Serum IgD levels in HIDS can be markedly increased (34, 39, 40, 68). Other biomarkers, for example, mevalonic acid activity and levels in the urine of patients with HIDS, the production of IL-1β by cultured monocytes in CAPS (69) and the serum level of soluble TNF receptor 1 in TRAPS (70), are not generally available and are performed mainly for research purposes. In Schnitzler's syndrome, an IgM paraprotein is typically present (41).

### Genetics

Molecular genetic diagnostic testing can confirm autoinflammatory disease (Table 2). A diagnostic flow chart for a rational application of this cost-intensive approach has been published (71).

Nonetheless, genetic tests must be interpreted in context, and a variety of issues should be considered when using genetic analyses to diagnose autoinflammatory diseases:

1 Up to 20% of patients with FMF do not exhibit two mutations within the *MEFV* gene (72, 73), but their clinical course resembles that of patients with a combined heterozygous or homozygous mutations (74). On the other hand, in certain ethnic groups, most subjects with two mutations within the *MEFV* gene do not suffer from clinical FMF (phenotype III FMF) (75, 76).
   Another challenge in the interpretation of genetic results are the occurrences of polymorphisms, especially of the amino acid exchange at MEFV position 148 (77). Thus, the diagnosis of FMF is still based on clinical grounds (42); but the genetic analysis can have a significant value in the confirmation of the suspected diagnosis and may allow a prediction on the disease course (78).
2 In patients with CAPS, the frequency of a negative genetic analysis of the *NLRP3* gene varies according to the subtype: in FCAS up to 10%, in MWS up to 25% and in NOMID up to 50% of patients do not exhibit mutations despite a characteristic clinical phenotype (60, 79).
3 TRAPS is defined as a disease caused by mutations within the *TNFRSF1A* gene (70). Low-penetrance polymorphisms (R92Q or P46L) are usually of no clinical significance, although R92Q is sometimes associated with a milder disease phenotype, which responds to less intensive treatments (80).
4 A definite diagnosis of mevalonate kinase deficiency or HIDS can be established when the mevalonate kinase deficiency is present. This can be determined directly by biochemical testing (raised mevalonic acid in the urine during a fever episode) or by genetic testing of the mevalonate kinase gene (81). The most prevalent mutations are V377I and I268T.
5 Like in FMF, patients exhibiting (some) clinical characteristics for TRAPS and HIDS but with no mutations in the relevant gene have been described (47, 82). It is currently a matter of debate whether these patients should correctly be classified as 'autoinflammatory disorder not otherwise specified'.

## Conclusions

The underlying causes of recurrent fever are manifold, and their identification is challenging. Autoinflammatory disorders often present with recurrent febrile attacks and consequently have to be considered when evaluating a patient with such a history of fever. Recognizing symptom patterns can provide crucial clues and, thus, lead to the initiation of targeted specific diagnostic tests and therapies.

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## Authors' contribution

All authors took part at the EAACI task force meeting on autoinflammatory disease held January 2011 in Berlin and were involved in the manuscript preparation.

## Conflict of interest

None.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Box 2: Infectious diseases causing recurrent fever in immunocompetent individuals.

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